

CLAIMS:

1. A method of inducing a dopaminergic neuronal fate in a
5 neural stem cell or neural progenitor cell, the method
comprising:
expressing *Nurr1* above basal levels within the cell,
and
contacting the cell with one or more factors obtainable from a
10 Type 1 astrocyte of the ventral mesencephalon, whereby
dopaminergic neurons are produced.
2. A method according to claim 1 comprising contacting the
cell with FGF8.
- 15 3. A method according to claim 1 comprising transforming a
neural stem cell or neural progenitor cell with *Nurr1*.
- Sub 20 4. A method according to any one of claims 1 to 3 comprising
co-culturing the neural stem cell or neural progenitor cell
with a Type 1 astrocyte of the ventral mesencephalon.
- 25 5. A method according to claim 4 wherein the Type 1
astrocyte is immortalized or is of an astrocyte cell line.
- Sub 25 6. A method according to any one of the preceding claims
wherein said cell is mitotic when it is contacted with said
one or more factors.
- 30 7. A method according to any one of the preceding claims
wherein said cell is additionally contacted with one or more
agents selected from the group consisting of: basic fibroblast
growth factor (bFGF), epidermal growth factor (EGF), an
activator of the retinoid X receptor (RXR), and 9-cis retinol.

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8. A method according to any one of the preceding claims wherein said cell is additionally contacted with a member of the FGF family of growth factors.

9. A method according to claim 8 wherein said cell is contacted with bFGF or EGF, and SR11237.

10. A method according to any one of the preceding claims wherein the neural stem cell or neural progenitor cell is pretreated with bFGF and/or EGF prior to contacting the cell with one or more factors obtainable from a Type 1 astrocyte of the ventral mesencephalon.

11. A method according to any one of the preceding claims further comprising formulating a dopaminergic neuron produced by the method into a composition comprising one or more additional components.

12. A method according to claim 11 wherein the composition comprises a pharmaceutically acceptable excipient.

13. A method according to claim 12 further comprising administering the composition to an individual.

14. A method according to claim 13 wherein the dopaminergic neuron is implanted into the brain of the individual.

15. A method according to claim 14 wherein the individual has Parkinson's disease.

16. A method according to any of claims 1 to 10 further comprising use of a dopaminergic neuron produced in accordance with the method in the manufacture of a medicament for

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treatment of an individual.

17. A method according to claim 16 wherein the medicament is for implantation into the brain of the individual.

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18. A method according to claim 17 wherein the individual has Parkinson's disease.

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19. A dopaminergic neuron produced in accordance with any one of claims 1 to 10.

20. A composition comprising a dopaminergic neuron according to claim 19.

15 21. A composition according to claim 20 comprising one or more additional components.

22. Use of a dopaminergic neuron according to claim 19 in a method of screening for an agent for use in treatment of a
20 neurodegenerative disease.

23. A method according to any one of claims 1 to 10 further comprising:

25 (i) treating a dopaminergic neuron with a toxin for said dopaminergic neuron;

(ii) separating the dopaminergic neuron from the toxin;

(iii) bringing the treated dopaminergic neuron into contact with a test agent or test agents;

30 (iv) determining the ability of the dopaminergic neuron to recover from the toxin;

(v) comparing said ability of the dopaminergic neuron to recover from the toxin with the ability of a dopaminergic neuron to recover from the toxin in the absence of contact with the test agent(s).

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24. A method according to any one of claims 1 to 10 further comprising:

5 (i) treating a dopaminergic neuron with a toxin for the dopaminergic neuron in the presence of a test agent or test agents;

(ii) determining the ability of the dopaminergic neuron to tolerate the toxin;

10 (iii) comparing said ability of the dopaminergic neuron to tolerate the toxin with the ability of a dopaminergic neuron to tolerate the toxin in the absence of contact with the test agent(s).

25. A method according to claim 23 or claim 24 further comprising formulating an agent which improves ability of a dopaminergic neuron to recover from or tolerate a said toxin into a composition comprising one or more additional components.

20 26. A method according to claim 25 wherein said composition comprises a pharmaceutically acceptable excipient.

27. A method according to claim 26 further comprising administering said composition to an individual.

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28. A method according to claim 27 wherein the individual has Parkinson's disease.

30 29. A method of screening for a receptor or receptors for the factor or factors which are obtainable from Type I astrocytes of the ventral mesencephalon and which induce a dopaminergic fate in neural stem or progenitor cells expressing Nurr-1 above basal levels, the method comprising comparing neural stem or progenitor cells with or without expression of Nurr-1

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above basal levels within the neural stem or progenitor cells, to identify said receptor or receptors.

30. A method as in claim 29 which further comprises isolating and/or purifying and/or cloning said receptor or receptors.

31. A method as in claim 30 which further comprises using said receptor or receptors in a method of screening for said factors or factors obtainable from type I astrocytes of the ventral mesencephalon.

32. A method of screening for a factor or factors which, either alone or in combination, induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr1* above basal levels, the method comprising:

(a) bringing Type 1 astrocyte molecules into contact with a neural stem cell or neural progenitor cell expressing *Nurr1* above basal levels, which contact may result in interaction between the Type 1 astrocyte molecules and the neural stem or progenitor cell; and

(b) determining interaction between the Type 1 astrocyte molecules and the stem or progenitor cell.

33. A method according to claim 22 which comprises comparing molecules of Type 1 astrocytes of the ventral mesencephalon with those of neural cells which are unable to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr1* above basal levels.

34. A method of screening for a factor or factors which, either alone or in combination, induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr1* above basal levels, the method comprising culturing a neural stem cell or

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neural progenitor cell expressing *Nurr1* above basal levels in the presence of Type 1 astrocyte molecules and analyzing said cell for differentiation to a dopaminergic phenotype.

5 35. A method according to claim 34 which comprises comparing Type 1 astrocytes of the ventral mesencephalon with neural cells which are unable to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr1* above basal levels.

10 36. A method according to claim 33 which comprises differential expression screening.

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15 37. A method according to any one of claims 31 to 36 wherein a factor or factors able to induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr1* above basal levels is or are provided in isolated and/or purified form.

38. A method according to any one of claims 31 to 37 wherein a factor or factors able to induce a dopaminergic fate in a
20 neural stem or progenitor cell expressing *Nurr1* above basal levels is or are formulated into a composition comprising one or more additional components.

39. A method according to claim 38 wherein the composition
25 comprises a neural stem or progenitor cell expressing *Nurr1* above basal levels.

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30 40. A method according to claim 38 or claim 39 wherein the composition comprises a pharmaceutically acceptable excipient.

41. A method according to claim 40 further comprising administering the composition to an individual.

42. A method according to claim 41 wherein the composition is

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implanted into the brain of the individual.

43. A method according to claim 42 wherein the individual has Parkinson's disease.

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44. A method according to any one of claims 31 to 37 further comprising use of a factor or factors able to induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr1* above basal levels in the manufacture of a medicament for treatment of an individual.

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45. A method according to claim 44 wherein the medicament comprises a neural stem or progenitor cell expressing *Nurr1* above basal levels.

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46. A method according to claim 44 or claim 45 wherein the medicament is for implantation into the brain of the individual.

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47. A method according to claim 46 wherein the individual has Parkinson's disease.

48. A method of screening for a substance which modulates the ability of Type 1 astrocytes of the ventral mesencephalon, or a molecule or molecules of such astrocytes, to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr1* above basal levels, the method comprising:

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(i) co-culturing Type 1 astrocytes with neural stem or progenitor cells which express *Nurr1* above basal levels in the presence of one or more test substances; or

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(ii) bringing neural stem or progenitor cells which express *Nurr1* above basal levels into contact with one or more molecules of Type 1 astrocytes able to induce a dopaminergic phenotype in such cells, said contact occurring in the

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presence of one or more test substances;
and

(iii) analysing the proportion of stem or progenitor cells which adopt a dopaminergic fate;

5 (iv) comparing the proportion of stem or progenitor cells which adopt a dopaminergic fate with the number of stem or progenitor cells which adopt a dopaminergic fate in comparable reaction medium and conditions in the absence of the test substance(s).

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49. A method according to claim 48 wherein a substance which modulates the ability of Type 1 astrocytes of the ventral mesencephalon, or a molecule or molecules of such astrocytes, to induce a dopaminergic fate in neural stem or progenitor
15 cells expressing *Nurr1* above basal levels, is provided in isolated and/or purified form.

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50. A method according to claim 48 or claim 49 wherein a substance which modulates the ability of Type 1 astrocytes of the ventral mesencephalon, or a molecule or molecules thereof, to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr1* above basal levels, is formulated into a composition comprising one or more additional components.

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51. A method according to claim 50 wherein the composition comprises a pharmaceutically acceptable excipient.

52. A method according to claim 51 further comprising administering the composition to an individual.

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53. A method according to claim 52 wherein the composition is implanted into the brain of the individual.

54. A method according to claim 53 wherein the individual has

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Parkinson's disease.

55. A method according to claim 48 or claim 49 further comprising use of a substance which modulates the ability of
5 Type 1 astrocytes of the ventral mesencephalon, or a molecule or molecules of such astrocytes, to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr1* above basal levels, in the manufacture of a medicament for treatment of an individual.

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56. A method according to claim 55 wherein the medicament is for implantation into the brain of the individual.

57. A method according to claim 56 wherein the individual has
15 Parkinson's disease.

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